EXHIBIT A137

Systematic Review and Meta-Analysis of the Association between Perineal Use of Talc and Risk of Ovarian Cancer

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Abstract

Over the past four decades, there has been increasing concern that perineal use of talc powder, a commonly used personal care product, might be associated with an increased risk of ovarian cancer.

Objectives: To systematically review all available human epidemiological data on the relationship between perineal use of talc powder and ovarian cancer, with consideration of other relevant experimental evidence.

Methodology: We identified 30 human studies for qualitative assessment of evidence, including 27 that were retained for further quantitative analysis.

Results: A positive association between perineal use of talc powder and ovarian cancer was found [OR: 1.28 (95% CI: 1.20 - 1.37)]. A significant risk was noted in Hispanics and Whites, in women applying talc to underwear, in pre-menopausal women and in post-menopausal women receiving hormonal therapy. A negative association was noted with tubal ligation.

Conclusion: Perineal use of talc powder is a possible cause of human ovarian cancer.

Keywords: Talc; ovarian cancer; perineal; epidemiological studies; systematic review; meta-analysis; toxicological studies.

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1. Introduction

Ovarian cancer is a common gynecologic cancer among women in developed countries, occurring at low rates among young women but increasing with age [1]. The annual incidence rate of ovarian cancer during the period 2005 – 2009 was 12.7/100,000 women, varying by ethnicity. The majority of ovarian cancers are diagnosed at an advanced stage, with 61% having distant metastases at diagnosis. Hereditary risk factors for ovarian cancer, specifically BRCA1 gene mutations, increase the risk above 35 years of age by about 2-3%.

In recent decades, there has been increasing concern that perineal exposure to talc, a commonly used personal care product, might be associated with an increased risk of ovarian cancer. However, the data describing this association is somewhat inconsistent. Perineal application of talc among women varies by geographic location (Supplementary Material I), with prevalence of use generally higher in Canada, the US and the UK compared to Greece, China and Israel [2].

In order to better characterize the potential ovarian cancer risk associated with perineal use of talc, we conducted a systematic review and meta-analysis of peer-reviewed human studies on this issue. We also examined additional in-vitro or in-vivo toxicological studies, which shed light on possible biological mechanisms that might support an association between and ovarian cancer.

2. Materials and Methods

2.1. Literature Search and Identification of Relevant Human Studies

A comprehensive, multi-step search strategy was used to to identify relevant studies on talc from multiple bibliographic databases, relevant national and international agencies and other grey literature sources (Supplementary Material II). Specifically, conducted a systematic search for all original studies involving human subjects that examined the association of genital/perineal use of talc powder and risk of ovarian cancer, including studies identified in a previous review by Berge et al. [3]. This review followed the PRISMA guidelines, and more specific guidance provided by the Cochrane Collaboration [4] (see Supplementary Material II for details).

Included studies were individually evaluated and scored by two reviewers (MT and NF), as detailed in the Table 1 and Supplementary Material XI. Studies included in previous reviews by both Berge et al. [3] and Penninkilampi et al [5] are compared in Supplementary Material I.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) [6], as detailed in Supplementary Material IV. We used a cut-off point of 7+ stars to represent studies of higher quality.

2.2. Literature Search and Identification of Relevant Non-Human Studies

We conducted a (non-systematic) review of relevant non-human studies identified in three major bibliographic databases to identify potentially relevant animal

and in vitro studies (Supplementary Material V). Only studies that focused on perineal exposure to talc powder were included. For outcomes, studies that focused on any type of cancer including ovarian cancer and perineal exposure were considered. All retrieved studies were examined for relevance, reliability and overall quality using the Klimisch scoring system [7, 8] (Supplementary Material VII, VIII and IX).

Studies are classified into one of the following four categories of reliability: 1) reliable without restriction, 2) reliable with restrictions, 3) not reliable and 4) not assignable. Additionally, category (5) is assigned to special studies focusing on pharmacologic or mechanistic investigations.

2.3. Hazard Characterization

Epidemiological studies included in the systematic review were qualitatively assessed to examine their potential to inform a weight of evidence analysis. Findings from these studies were evaluated with respect to study design, exposure and outcome ascertainment, as well as potential sources of bias and confounding.

Animal studies were evaluated for evidence on the association between perineal application of talc and ovarian cancer. Additional information on mechanism of action and toxicokinetics derived from in-vitro and in-vivo studies was used in evaluating biological plausibility.

We evaluated the overall weight of scientific evidence by performing a qualitative evaluation of the findings collected from epidemiological studies as well as non-human studies, using the Hill criteria [9].

2.4. Quantitative Meta-Analysis

We conducted a meta-analysis of the risk of ovarian cancer in relation to perineal use of talc using quantitative risk estimates reported in 27 original studies, comprising three cohort studies and twenty-four case-control studies (included in Table 1). Studies that had analyzed overlapping study populations were assessed on a case-by-case basis for inclusion into the meta-analysis. The level of detail in the reported findings, including sample size and publication date, were considered when deciding which study to include in the case of overlap (Supplementary Material XIV).

Maximally adjusted odds ratios (ORs), hazard ratios (HRs) or relative risks (RRs) – measures that are largely comparable because of the relatively low rate of occurrence of ovariaion cancer – were extracted from the original studies. Details of the meta-analytic methods are provided in Supplementary Material XIV.

114 **Table 1: Characteristics and overall findings of all included studies (N=30).**

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
Case-control studies						
Booth et al.* (1989), UK [10]	235/451	Range: 20-65 Mean: 52.4 (cases); 51.4 (controls)	Frequency	No trend found	Possible association with >weekly use.	5
Chang and Risch (1997), Canada [11]	450/564	Range: 35-79 Mean: 57.2 (cases); 57.5 (controls)	Ever use Frequency Duration Time of use Type of use	Possible exposure-response with frequency and duration of use	Positive association	7

[1] Newcastle-Ottawa Scale (NOS) score for each of the listed studies as assessed in our review

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
			Pelvic surgery Histology			
Chen et al.* (1992), China [12]	112/224	Mean: 48.5 (cases); 49.0 (controls)	Ever use;	No trend analysis conducted	Positive association with use >3 months	6
Cook et al. (1997), USA [13]	313/422	Range: 20-79	Ever use Duration Type of use Histology Lifetime applications	No trend found	Positive association.	7
Cramer et al. (1982), USA [14]	215/215	Range: 18-80 Mean ± SD: 53.2 ± 1.0 (cases); 53.5 ± 1.0 (controls)	Ever use Type of use Pelvic surgery	No trend analysis conducted	Positive association	6

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
Cramer et al. (2016), USA [15]	2,041/2,100	Range: 18-80	Ever use; Frequency; Duration; Type of use; Histology; Type of powder; Pelvic surgery; Ethnicity; Age at first use; Time since last exposure;	Significant trend for years since exposure, frequency and duration of use, and number of lifetime applications	Positive association	7
Gates et al. (2008), USA [16]	New England Case Control (NECC): 1,175/1,202 Nurses' Health	Mean ± SD: 51 ±13 (NECC); Mean ± SD: 51 ±8 (NHS)	Ever use; Frequency;	Significant trend for frequency of use	Positive association	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
	Study (NHS): 210/600					
Godard et al. (1998), Canada [17]	153/152	Mean: 53.7	Ever use; Sporadic/familial	No trend analysis conducted	No association	5
Green et al. (1997), Australia [18]	824/860	Range: 18-79	Ever use; Pelvic surgery;	No trend found	Positive association	7
Harlow et al. (1989), USA [19]	116/158	Range: 20-79	Ever use; Type of use; Type of powder;	No trend analysis conducted	No association	7
Harlow et al. (1992), USA [20]	235/239	Range: 18-76	Ever use; Frequency; Duration; Type of use;	Significant trend for monthly frequency of use	Positive associations in certain subgroups (talc used before 1960, women <50	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
			Method of use; Histology; Tumor grade; Type of powder; Lifetime applications; Age of first use; Pelvic surgery;		years old, women with 1 or 2 live births)	
Hartge et al. (1983), USA [21]	135/171	Mean: 52.1 (cases); 52.2 (controls)	Ever use;	No trend analysis conducted	No association	5
Kurta et al. (2012), USA [22]	902/1,802	Range: No range reported (age 25+)	Ever use;	No trend analysis conducted	Positive association	6
Langseth & Kjaerheim (2004), Norway [23]	46/179	Not reported	Ever use,	No trend analysis conducted	No association	4

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
Merritt et al. (2008), Australia [24]	1,576/1,509	Range: 18-79 Mean: 57.8 (cases); 56.4 (controls)	Ever use; Duration; Histology; Pelvic surgery; Age at diagnosis;	No trend found	Positive association strongest for serous and endometrioid subtypes.	7
Mills et al. (2004), USA [25]	249/1,105	Mean ± SD: 56.6 (cases); 55 (controls)	Ever use; Frequency; Duration; Year of first use; Histology; Pelvic surgery; Time of use; Tumor behavior; Cumulative use;	No trend found	Positive association for invasive and serous invasive tumors.	6

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
Moorman et al. (2009), USA [26]	African-American: 143/189; White 943/868	Range: 20-74	Ever use; Ethnicity;	No trend analysis conducted	No association	6
Ness et al. (2000), USA [27]	767/1,367	Range: 20-69	Ever use; Duration; Method of use;	No trend found	Positive association for any method of use.	6
Rosenblatt et al. (1992), USA [28]	77/46 (analyzed)	Range: ≤30 – 80≥	Ever use; Duration; Type of use; Pelvic surgery;	Positive trend for duration of use since tubal ligation	Possible association	4
Rosenblatt et al. (2011), USA [29]	812/1,313	Range: 35-74	Ever use; Lifetime number of applications; Duration;	No trend found	Possible association	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
			Year of first use; Age of first use; Age of last use; Time of use; Type of use; Histology;			
Schildkraut et al. (2016), USA [30]	584/745	Range: 20-79	Ever use; Frequency; Duration; Histology; Lifetime applications; Menopausal status;	Significant trend with frequency and duration of use, and number of lifetime applications	Positive association	8
Tzonou et al. (1993), Greece [31]	189/200	Range: <70	Ever use;	No trend analysis conducted	No association	5

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
Whittemore et al. (1988), USA [32]	188/539	Range: 18-74	Ever use; Frequency; Duration; Type of use; Pelvic surgery;	No trend found	Could neither implicate nor exonerate talc as an ovarian carcinogen	4
Wong et al. (1999, 2009), USA [33, 34]	462/693	Mean: 54.9	Ever use; Type of use; Duration; Pelvic surgery;	No trend found	No association	4
Wu et al. (2015), USA [35]	1,701/2,391	Range: 18-79	Ever use; Ethnicity;	No trend analysis conducted	Positive association among Hispanics and non-Hispanic whites, but not African Americans.	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
Wu et al. (2009), USA [34]	609/688	Range: 18-74	Ever use; Frequency; Duration; Type of use; Histology; Time of use; Cancer stage;	Significant trend for frequency and duration of use, and number of lifetime applications	Positive association	7
Cohort studies						
Gates et al. (2010)*, USA [36]	797/108,870	Range: 30-55	≥/week vs <1/week; Histology;	No trend analysis conducted	Possible association that varies by histological subtype. No association with mucinous tumors.	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[1]
Gertig et al. (2000), USA [37]	307/78,630	Range: 30-55 (at cohort entry)	Ever use; Frequency; Histology; Race;	No trend found	Possible association (modest increase for serous invasive subtype)	5
Gonzalez et al. (2016), USA [38]	154/41,654	Range: 35-74 Median: 57.8	Ever use; Time of use;	No trend analysis conducted	No association	6
Houghton et al. (2014), USA [39]	429/61,285	Range: 50-79 Mean: 63.3	Ever use; Duration; Type of use; Histology;	No trend found	No association	7

** Study assessed for qualitative evidence but not included in the meta-analysis*

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3. Results

3.1. Evidence from Human Studies

The multiple database search for original human studies yielded 656 references. Although grey literature search yielded another 477 references, only 5 were judged relevant the present analysis. Automatic followed by manual removal of duplicates identified 282 references for screening and review.

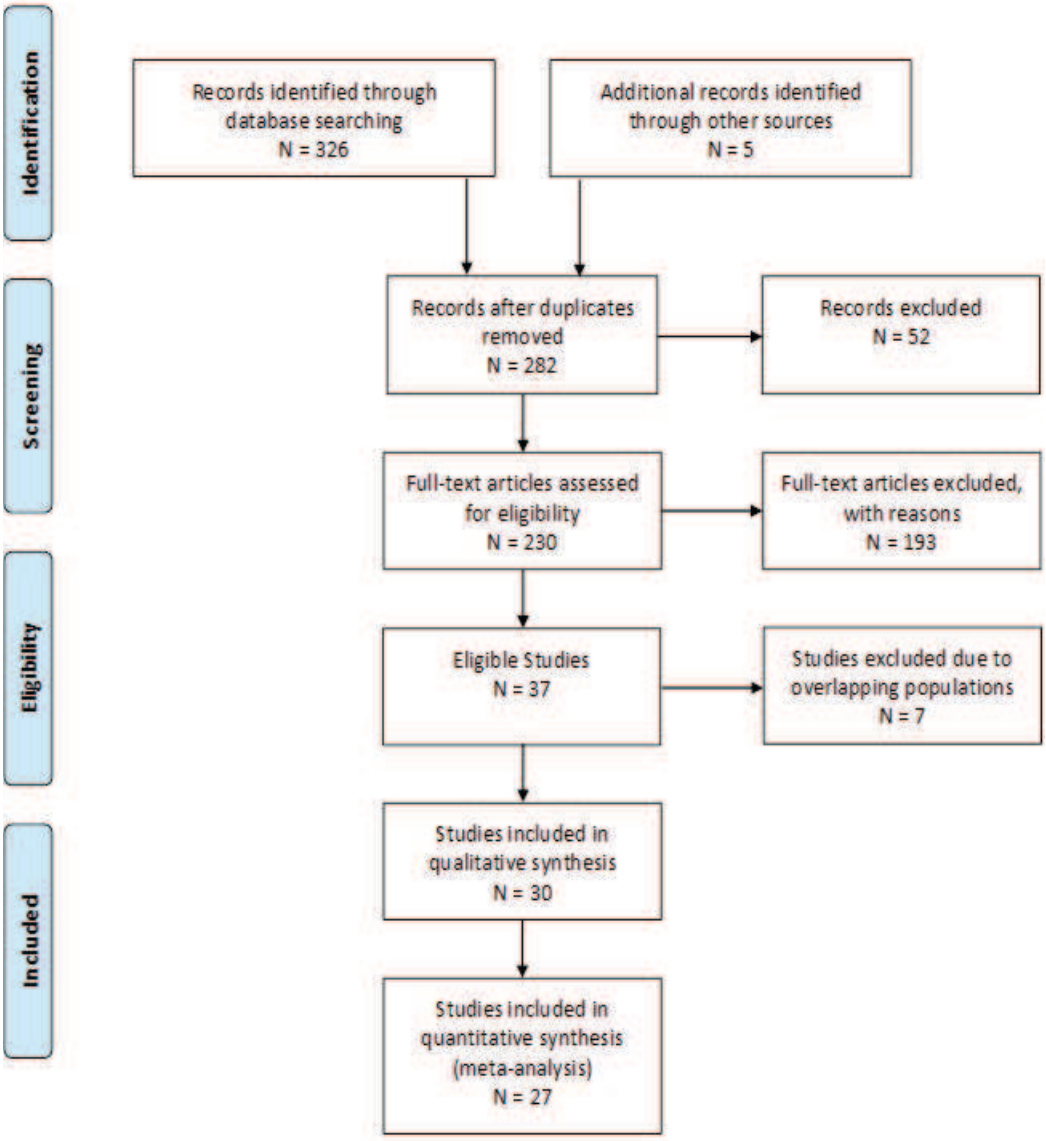
Multi-level screening and full-text examination resulted in the in the inclusion of 30 studies for further qualitative/quantitative analyses (Supplementary Materials X and XI). A detailed PRISMA flow diagram is shown in Figure 1 [40]. Key characteristics of the included 26 case-control studies and four cohort studies are summarized in Table 1.

Twenty-one of the thirty studies were carried out in the USA, with the remaining studies conducted in Europe (n=4), Canada (n=2), Australia (n=2) and China (n=1). Forty percent (n=12) of the studies were relatively recent, published in the last decade, with the remaining studies published between 1982 and 2006. The study populations generally included adult women. Several studies analyzed data from populations initially recruited for other purposes, such as the Nurses' Health Study (NHS) [15, 36, 37] and Women's Health Initiative (WHI) [39].

The number of ovarian cancer patients analyzed varied from as few as 46 cases [23] to 22,041 cases [15]. Twenty-seven out of the 30 included studies assessed the association between ever use of perineal talc use and ovarian cancer. Subgroup

136 analyses examining the effect of frequency and duration of use, type of use, period of

137 use and other factors varied among these studies (Table 1).



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139 Figure 1: PRISMA Flow Diagram

140 Sixty three percent (n=19) of the studies concluded the presence of a positive

141 association between perineal exposure to talc powder and ovarian cancer risk [10-16,

18, 20, 22, 24, 25, 27-30, 34-36]. Ten studies concluded the absence of an association [17, 19, 21, 23, 26, 31, 33, 37-39]. Only one study could not reach a clear conclusion on the presence or absence of an association [32]. Many of the included studies reported variability in some of the analyzed subgroups regarding possible association between exposure to talk powder and risk of ovarian cancer. Supplementary Material X presents the findings and details of all the studies included in the analysis, while Supplementary Material XI summarizes the strengths and limitations of each of these studies as identified by the original study authors and by us.

3.2. Evidence from Non-Human studies

After removal of duplicates, the bibliographic database searches on non-human studies initially yielded 1,165 references. The 51 retained animal studies focusing on the carcinogenicity of talc, mechanism of action, and toxicokinetics are summarized in Supplementary Material XII.

3.3. Hazard Characterization

3.3.1. Evidence from Human Studies

The case-control studies generally included adult women participants. Cases were commonly selected from registries or hospital records, and included all eligible subjects within a specific geographic region and diagnosed with ovarian cancer within a predetermined time period. Controls were generally matched to cases by age and residence. All the included studies compared the risk of ovarian cancer in ever vs never

users of talc (perineal application). However, several of the studies also included subgroup analyses to examine the potential effect of frequency of use, duration of use, tumor histology, ethnicity, method of use, lifetime number of applications, year of first use, and menopausal status. Some authors concluded that the risk of ovarian cancer is limited to [or stronger in] certain subgroups (weekly talc users, premenopausal women) or for specific histology types (notably serous tumors).

Studies reported effect estimates adjusted for a variety of potential confounders (see detailed tables in Supplementary Material X & XI). Age and parity were considered the two most important variables that could introduce potential bias, based on prior literature: few studies reported findings that were not adjusted for these two variables. As many of the studies only reported on the ovarian cancer risk assessing only one exposure category (comparing only ever vs never users of talc), exposure-response analyses were not done in all studies. When conducted, findings from trend analyses were not consistent.

3.3.2. Evidence from Non-Human Studies

The following aspects were considered in the weight of evidence assessment of ovarian cancer and perineal exposure to talc:

- hazards arising from the physical and chemical properties of talc, including potential structure-activity relationship indicative of carcinogenic potential;
- the toxicokinetics of talc and the ability to migrate from the perineal area to ovaries and quantity at the actual target site (the tissue dose);

- evidence on ovarian cancer reported in animal studies; and
- findings from in vitro studies suggestive of mechanism of action of carcinogenic effect.

While the data from the animal studies considered various routes of talc administration are inconsistent [41-46], there are observations from in vivo and in vitro studies which support the potential for local carcinogenic action of talc on fallopian, ovarian and peritoneal epithelium [27, 47-53].

The results from the *in vitro* studies are informative for mechanisms of action of possible carcinogenicity. Smith and colleagues [54] identified 10 key characteristics (KCs) commonly exhibited by established human carcinogens.

Oxidative stress (KC 6) and inflammation (KC 5) in cell cultures induced by talc have been reported by several authors [48], corresponding to two of the 10 key characteristics (KCs) described by Smith et al. [54]. Several authors suggested additional potential mechanisms of action through cell proliferation (KC 10) and changes in gene expression, presumably facilitated by oxidative stress and dysregulated antioxidant defense mechanisms [49, 55].

Chronic perineal or vaginal exposures of animals to talc do not directly affect ovulation or steroidal hormone levels, but can induce chronic local inflammation, which has been suggested as a risk factor for ovarian cancer [56]. Mechanism of action studies suggested that talc can complex iron on the surface and disrupt iron homeostasis, associated with oxidant generation, macrophage distress and leukotriene

released by macrophages in the surrounding cells resulting in the inflammatory response which could act as a tumor promoter in both animals and humans [48, 50, 51].

The changes seen in cultured cells after exposure to talc [50, 51] are consistent with those inflammatory and proliferative processes in the lungs seen in laboratory animals after inhalation exposure in a 1993 study conducted by the US National Toxicology Program [47]. In female rats, hyperplasia of alveolar epithelium was associated with inflammatory response and occurred in or near foci of inflammation [47]. The severity of the fibrous granulomatous inflammation in the lungs increased with increased talc concentrations and exposure duration and a significant association was observed between inflammation and fibrosis in the lungs and the incidence of pheochromocytomas in this study [47]. Overall, the avaialbe experimental data suggest irritation, followed by oxidative stress and inflammation, may play be involved in local carcinogenic effects of talc in the ovaries.

Local inflammation of the epithelial ovarian surface in rats following by injection of a suspension of talc particles demonstrated the development of foreign body granulomas surrounding talc particles and large ovarian bursal cysts [53]. It is generally accepted that benign and malignant ovarian epithelial tumors arise from surface epithelium and its cystic derivatives, and surface epithelial cysts have a greater propensity to undergo neoplasia than does the surface epithelium itself [57]. Evidence of neoplasms of epithelial origin, nuclear atypia, or mitotic activity in the surface epithelium was not found in this study; however, focal areas of papillary changes in the surface epithelium consistent with the histological signs of premalignancy were observed in 40% of treated animals [53].

Data on talc migration in the genital tract of animals is inconsistent, but could not exclude such possibility [58-61]. Some studies have reported lack of neutron-activated talc migration from the vagina to the ovaries in cynomolgus monkeys [58], but talc particles were identified in the ovaries of rats that received intrauterine instillation of talc [60]. Radioactivity was not found in the ovaries of rabbits dosed intravaginally with tritium-labelled talc, but was detected in cervix and fallopian tubes [59-61]. In studies in humans, Henderson and colleagues [62] examined tumor tissue of female patients with ovarian and cervical tumors. The authors detected talc particles in histological samples from 10 of 13 ovarian tumors, 12 of 21 cervical tumors and in 5 samples of 12 normal ovarian tissues [62].

Historically, the concern for talc carcinogenicity has been associated with its contamination by asbestos fibers (tremolite) [63], which is considered carcinogenic to humans [2]. Talc, including baby powder, available in the US, contains only U.S. Pharmacopeia (USP) grade pure talc [64]. Talcum powder has been asbestos-free since the 1976 where the specifications for cosmetic talc were developed [65].

3.3.3. Weight of evidence for carcinogenicity

Based on our evaluation of the weight of multiple lines of evidence, we concluded that perineal application of talc is a possible casue of cancer ovarian cancer in humans. In 2010 the Internatinal Agency for Research on Cancer [2] categorized perineal use of talc-based body powder (not containing asbestos or asbestiform fibers) as “possibly carcinogenic to humans (Group 2B)” [66].

Table 2 summarizes the available evidence for the association of ovarian cancer with perineal application of talc, organized around the nine Hill criteria [9]. Additoinal details of this evaluation are given in Supplementary Material XIII.

Table 2: Summary of evidence for each of the Hill Criteria of causation, as applied to perineal application of talc and ovarian cancer

Criterion	Summary of Evidence
Strength of association	• Out of the 30 epidemiological studies, six reported positive association of statistical significance with a risk value (relative risk or odds ratio) of 1.5 or greater • None of the cohort studies (n=3) found statistically significant association
Consistency	Fifteen out of thirty studies reported positive and significant associations reported in: • Different ethnicities (Caucasians, African Americans, and Latin Americans); • Over four decades (1982 - 2016); • Mostly in studies from the United States but also in other countries (Canada, Australia and China) • Case-control studies but not in cohort studies
Specificity	• Overall, the perineal talc exposure is specifically associated with cancer of the ovary and not other organs • No evidence of other target organs (e.g., liver) being associated with perineal application of talc (via systemic exposure)

Criterion	Summary of Evidence
	• Thirteen studies included analyses by histologic type of ovarian cancer, and eight of them found a significant increase in the risk of serous ovarian cancer in talc users
Temporality	• In all case-control studies reporting positive outcome, the participants recalled that exposure to talc preceded the reported outcome • In cohort studies, the follow up period could have been inadequate (<15 years) to detect a potential association between talc exposure and ovarian cancer
Biological gradient (exposure-response)	• About half of the epidemiological studies assessed only one level of talc exposure (ever vs never usage) • Of the 12 studies reporting a positive association, six studies found significant exposure-response trend, particularly with medium and high frequency usage groups Regarding duration of use/exposure to talc, several studies reported the greatest risk in the 20+ years of use exposure group, followed by the 10-20 years' group, then the <10 years' group
Biological plausibility	• Particles of talc appear to migrate into the pelvis and ovarian tissue causing irritation and inflammation • Transport of talc via perineal stroma and presence in ovaries documented • Chronic inflammatory response and alteration in local immunogenicity are possible mechanisms
Coherence	• Results from talc epidemiology studies are coherent with the current knowledge on the risk factors for ovarian cancer (e.g., factors/physiological states associated with greater frequency and duration of ovulation are associated with increased risk of ovarian cancer)

Criterion	Summary of Evidence
	• Many (but not all) case-control studies reported lower risk of ovarian cancer in women who underwent pelvic surgery or tubal ligation (which disrupts the pathway and movement of talc from lower to upper genital tract) & suppressed ovulation
Experimental evidence	• Perineal application of talc has not been tested in an animal model of ovarian cancer • The single animal cancer bioassay with talc conducted by the US National Toxicology Program was only by the inhalation route • Rodent models may be of limited relevance because of ovulations occurring only or mainly during the breeding season and the rarity of ovarian epithelial tumors in these animals and ovaries are variously enclosed in an ovarian bursa.
Analogy	• Talc and asbestos are both silicate minerals • Talc has been variably contaminated with asbestos (tremolite and anthophyllite; until 1976, talcum powders were only required to contain at least 90% mineral talc) • The pleural and peritoneal mesotheliomas caused by asbestos are histologically similar to epithelial ovarian cancer associated with talc • In animal models, asbestos induces ovarian epithelial hyperplasia similar to early epithelial tumors reported in women with past use of talc

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3.4. Meta-Analysis

The use of genital talc was associated with a significant increase in the risk of epithelial ovarian cancer, with an overall odds ratio [OR] based on our meta-analysis of 1.28 (95% confidence interval [CI]: 1.20 to 1.37 P<0.0001, I^2= 33%), as presented in

Figure 2. This result is comparable to those of earlier meta-analyses conducted by other investigators [3, 5, 67-69] as shown in Supplementary Material I.

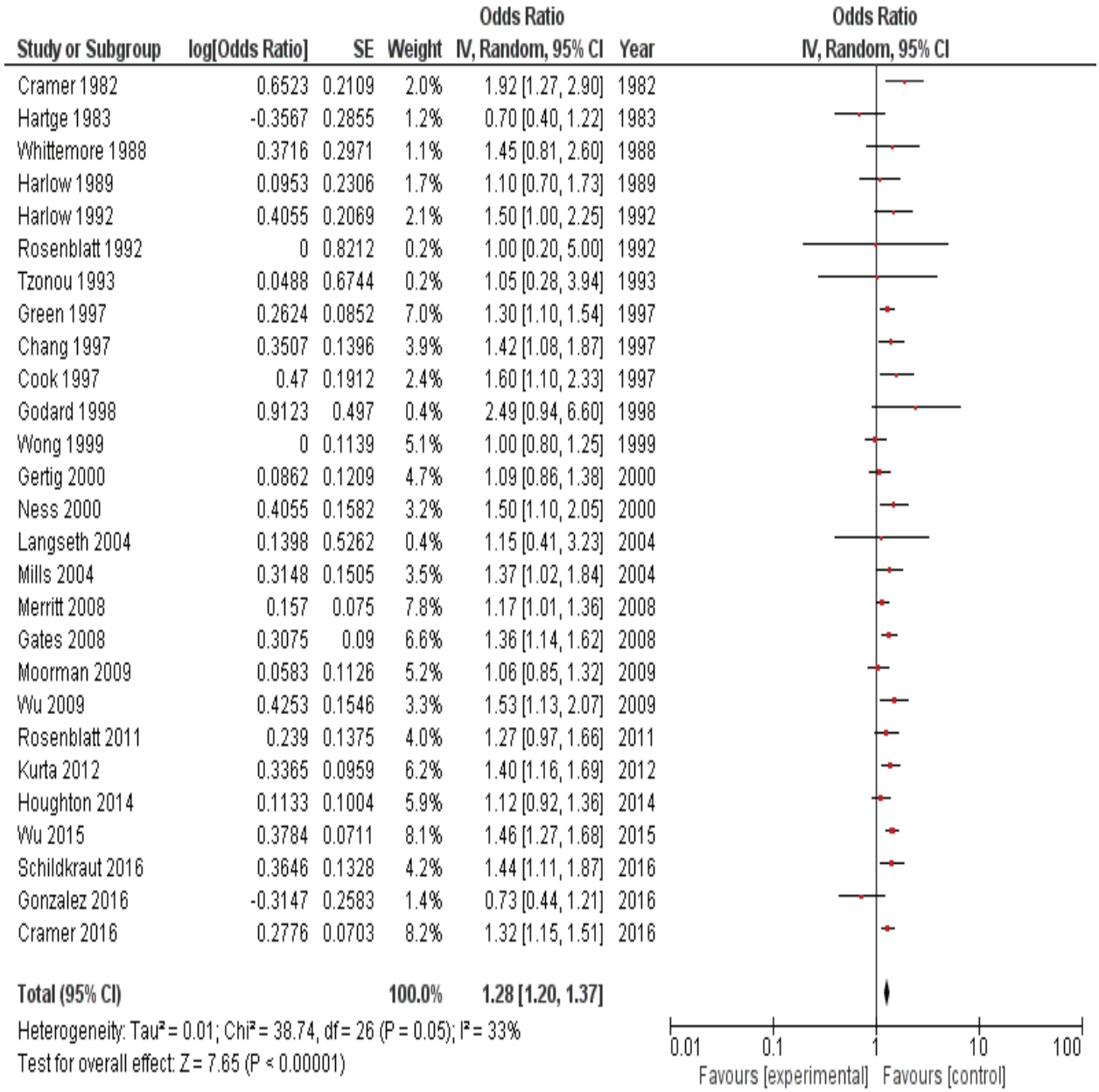

FIGURE 2: Forest plot of the meta-analysis results on perineal use of talc and risk of ovarian cancer

An increased risk is more apparent in Hispanics and Whites, in women applying talc to underwear, in pre-menopausal women and post-menopausal women receiving hormonal therapy, as well as for the serous and endometrioid types of ovarian cancer (Table 3 and Supplementary Material XIV). A negative association was noted with tubal ligation. Our analysis pooled risk estimates from 27 original studies including 3 cohort studies and 24 case-control studies, spanning across four decades (1982-2016) and including a total of 16,352 cases and 19,808 controls from different ethnicities.

In assessing heterogeneity among included studies, most subgroup analyses reported an I^2 statistic ranging between 0%-40%, which will have only a minimal impact on the analysis [4]. Only three subgroup analyses (ethnicity, menopausal state, and pelvic surgery) reported an I^2 statistic of 77%-78%, where considerable heterogeneity might have had an impact on the results [4]. (See Table 3 and Supplementary Material XIV for a listing of I^2 statistic values for the different subgroup analyses)

Whereas case-control studies showed a significant increase in the risk of ovarian cancer for ever vs never users of talc powder [OR: 1.32 (95% CI: 1.24 to 1.40), P < 0.00001, I^2= 22%], cohort studies failed to show a significant increase in risk [OR: 1.06 (95% CI: 0.9 to 1.25), P= 0.49, I^2= 17%]. Thirteen out of 24 case-control studies (54%) showed a statistically significant association, whereas none of the 3 cohort studies showed a significant overall association between ever vs never genital talc exposure and risk of ovarian cancer.

Subgroup analysis by study quality (NOS≥7 vs NOS<7) did not show any significant differences in the overall pooled risk estimate. Similarly, there were no differences among subgroup analysis conducted by decade of publication. A significant association was observed for population-based studies [OR: 1.34 (95% CI: 1.27 to 1.41), P < 0.00001, I^2= 0%], but for enlisting hospital-based controls [OR: 0.96 (95% CI: 0.78 to 1.17), P= 0.66, I^2= 0%].

We conducted influence analysis to examine the impact of individual studies on the results of our meta-analysis. No appreciable changes were observed regarding the overall association of perineal talc exposure and the risk of ovarian cancer in response to the exclusion of any one study. Detailed results from the influence analysis are provided (Supplementary Material XIV).

Subgroup analysis based on ethnicity indicated that Hispanic women using talc showed the most significant increase in risk of ovarian cancer [OR: 1.70 (95% CI: 1.17 to 2.47), P = 0.005, I^2= 0%], followed by White women [OR: 1.28 (95% CI: 1.10 to 1.49], P= 0.001, I^2= 56%). African-American women showed a non-significant association with ovarian cancer in [OR: 1.67 (95% CI: 0.90 to 3.10), P= 0.1, I^2= 48%].

Analyzing exposure by frequency of talc use, talc exposure was stratified into three groups: high (once daily for >25 days/month), medium (once daily for 10–25 days/month) and low (once daily for 1–<10 days/month). The OR for the high-use group was higher in the high-use group compared to the other two groups (medium and low-use groups). Duration of talc use was stratified into three groups: <10 years, 10 – <20 years, and 20+ years. The overall odds ratio of the <10 years' group was lower than the

OR for the 10 – <20 years' group. On the other hand, the OR for the 20+ years' group was lower and not statistically significant. However, this OR was based on two studies that showed considerable heterogeneity (I^2=75%). Examining the method of application of talc, application to the underwear subgroup had a statistically significant OR, which was the highest among all subgroups. Diaphragm use showed an expected, yet non-significant, negative association with ovarian cancer, which may be due to its action blocking the ascent of talc particles up the reproductive tract.

Pooled risk estimates were statistically significant for two histological types of ovarian cancer: serous tumors [OR: 1.38 (95% CI: 1.22 to 1.56), P < 0.00001, I^2= 0%] and endometrioid tumors [OR: 1.39 (95% CI: 1.05 to 1.82), P= 0.03, I^2= 2%]. The mucinous type showed a non-significant association [OR: 1.05 (95% CI: 0.85 to 1.29), P= 0.41, I^2= 23%], while there were not sufficient studies to examine the other types of ovarian cancers. Regarding tumor behavior, there was no appreciable difference between invasive [OR: 1.38 (95% CI: 1.15 to 1.65), P= 0.0004, I^2= 0%] and borderline [OR: 1.43 (95% CI: 1.08 to 1.89), P= 0.01, I^2= 19%] grades of ovarian cancer. Borderline serous tumors showed slightly greater risk [OR: 1.39 (95% CI: 1.09 to 1.78), P= 0.008, I^2= 0%] compared to the serous invasive grade [OR: 1.32 (95% CI: 1.13 to 1.54), P= 0.0004, I^2= 24%], while both showed a significant association with perineal talc exposure. However, the mucinous tumors showed a non-significant association with talc exposure, with invasive grades being associated with a greater risk [OR: 1.34 (95% CI: 0.48 to 3.79), P= 0.58, I^2= 70%] compared to the borderline grade [OR: 1.18 (95% CI: 0.76 to 1.82), P < 0.46, I^2= 34%].

Among post-menopausal women, those receiving hormonal therapy showed the greatest risk [OR: 2.28 (95% CI: 1.72 to 3.01), P < 0.00001, I^2= 0%], followed by pre-menopausal women [OR: 1.42 (95% CI: 1.16 to 1.75), P= 0.0008, I^2= 0%], and then post-menopausal women not receiving hormonal therapy [OR: 1.05 (95% CI: 0.84 to 1.32), P= 0.66, I^2= 25%]. This subgroup analysis suggests that hormonal factors, especially estrogens influence the risk of developing ovarian cancer among postmenopausal women who have perineal talc exposure.

Women with prior ligation of the Fallopian tubes showed a significant reduction in risk [OR: 0.64 (95% CI: 0.45 to 0.92), P= 0.02, I^2= 19%] against ovarian cancer compared to hysterectomy [OR: 0.89 (95% CI: 0.54 to 1.46), P= 0.65, I^2= 61%], whereas both surgeries combined showed no effect [OR: 1.06 (95% CI: 0.78 to 1.42), P= 0.72, I^2= 61%]. This might be attributed to the fact that tubal ligation is usually performed at an earlier age, thus preventing entry of talc into the reproductive tract earlier and prolonged exposure to talc, compared to hysterectomy that is performed later in life where a higher exposure has already taken place. In a recent meta-analysis [70], the authors reported a negative association of tubal ligation (27 studies) and hysterectomy (15 studies) with the risk of ovarian cancer: this negative association was more apparent in women who had the surgery at an earlier age. A highly plausible mechanism for this association, as suggested by the authors, involves blocking of ascent of agents such as talc to the ovaries.

A summary of results of our meta-analysis is shown in Table 3. Forest plots of all sub-group analyses are provided in Supplementary Material XIV.

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359 **Table 3: Results of the subgroup analysis of talc exposure and ovarian cancer**

Outcome or Subgroup	Studies	Effect Estimate [95% CI)	Heterogeneity I^2 Statistic [p-value]
1. Talc use			
Ever vs. Never	27	1.28 [1.20, 1.37]	33% [< 0.00001]
Ethnicity	3		77% [0.08]
African Americans	3	1.67 [0.90, 3.10]	48% [0.10]
Hispanics	2	1.70 [1.17, 2.47]	0% [0.005]
Whites	3	1.28 [1.11, 1.49]	56% [0.001]
Asians	1	0.04 [0.01, 0.16]	N/A
2. Study Assessment			
2.1. Study Design	27		33% [< 0.00001]
Case-Control	24	1.32 [1.24, 1.40]	22% [< 0.00001]
Cohort	3	1.06 [0.90, 1.25]	17% [0.49]
2.2. Type of Controls	24		22% [< 0.00001]
Hospital-based	4	0.96 [0.78, 1.17]	0% [0.66]
Population-based	19	1.34 [1.27, 1.41]	0% [< 0.00001]
Combined	1	1.45 [0.81, 2.60]	N/A
2.3. Quality Score (NOS)	27		33% [< 0.00001]
NOS >=7	12	1.32 [1.25, 1.40]	0% [< 0.00001]
NOS <7	15	1.21 [1.05, 1.39]	47% [0.009]
2.4. Publication Year	27		33% [< 0.00001]
1980-1989	4	1.23 [0.81, 1.88]	66% [0.33]
1990-1999	8	1.30 [1.13, 1.50]	24% [0.0003]
2000-2009	8	1.25 [1.14, 1.37]	18% [< 0.00001]
2010 and beyond	7	1.31 [1.18, 1.45]	44% [< 0.00001]
3. Talc Exposure			
3.1. Frequency of Use	7		35% [< 0.00001]
Low	5	1.22 [0.96, 1.54]	54% [0.10]
Medium	2	1.22 [0.98, 1.53]	0% [0.08]
High	7	1.39 [1.22, 1.58]	23% [< 0.00001]
3.2. Duration of Use	6		5% [0.0008]
<10 Years	5	1.22 [1.03, 1.45]	0% [0.02]

Outcome or Subgroup	Studies	Effect Estimate [95% CI)	Heterogeneity I^2 Statistic [p-value]
10 - <20 Years	2	1.42 [1.02, 1.99]	0% [0.04]
20+ Years	2	1.19 [0.71, 1.98]	75% [0.51]
3.3. Method of Use	13		52% [0.001]
Sanitary Napkin	11	1.12 [0.91, 1.39]	50% [0.29]
Diaphragm	10	0.87 [0.72, 1.05]	25% [0.14]
Underwear	2	1.70 [1.27, 2.28]	0% [0.0004]
Male Condom	3	0.99 [0.73, 1.32]	0% [0.92]
4. Tumor Histology			
4.1. Tumor Histology	8		23% [< 0.00001]
Serous	7	1.38 [1.22, 1.56]	0% [< 0.00001]
Mucinous	5	1.05 [0.85, 1.29]	23% [0.41]
Endometrioid	6	1.39 [1.05, 1.82]	2% [0.03]
Clear Cell	1	0.63 [0.15, 2.65]	
5. Tumor Behavior			
5.1. All Grades	4		0% [< 0.00001]
All Invasive	3	1.38 [1.15, 1.65]	0% [0.0004]
All Borderline	4	1.43 [1.08, 1.89]	19% [0.01]
5.2. Serous	5		0% [< 0.00001]
Serous Invasive	5	1.32 [1.13, 1.54]	24% [0.00004]
Serous Borderline	3	1.39 [1.09, 1.78]	0% [0.008]
5.3. Mucinous	3		38% [0.40]
Mucinous Invasive	2	1.34 [0.48, 3.79]	70% [0.58]
Mucinous Borderline	3	1.18 [0.76, 1.82]	34% [0.46]
5.4. Endometrioid	1		N/A
Endometrioid Invasive	1	1.38 [1.06, 1.80]	
5.5. Clear Cell	1		N/A
Clear Cell Invasive	1	1.01 [0.65, 1.57]	
6. Modifiers			
6.1. Menopausal State	2		78% [0.007]
Pre-menopausal	2	1.42 [1.16, 1.75]	0% [0.0008]
Post-Menopausal (HT)	2	2.28 [1.72, 3.01]	0% [< 0.00001]
Post-Menopausal (no HT)	2	1.05 [0.84, 1.32]	25% [0.66]

Outcome or Subgroup	Studies	Effect Estimate [95% CI)	Heterogeneity I^2 Statistic [p-value]
6.2. Pelvic Surgery	7		78% [0.35]
Tubal Ligation	3	0.64 [0.45, 0.92]	19% [0.02]
Hysterectomy	4	0.89 [0.54, 1.46]	61% [0.65]
Combined	4	1.06 [0.78, 1.42]	61% [0.72]

*** NOS:** Newcastle-Ottawa Scale for quality scoring of observational studies

**** Low:** Once daily for 1 – <10 days/month; **Medium:** Once daily for 10 –25 days/month; **High:** Once daily for >25 days/month

3.5. Exposure-Response Assessment

The effect of increasing frequency or duration of perineal use of talc and the risk of ovarian cancer was assessed in the majority of the studies included in this review. Conflicting findings were reported on the nature of the exposure-response relationship: 11 studies concluded that there is no exposure-response, five studies reported a significant positive trend with either frequency or duration of talc use, and two studies concluded that there might be an exposure-response. The remaining twelve studies did not perform or report on trend analyses.

Findings from the seven studies that indicated a potential increased risk of ovarian cancer associated with increasing use of talc are presented in Table 4. The study by Cramer et al. [15] provides the strongest evidence of an exposure-response relationship and could be considered as a key study for exposure-response assessment. The data used in this study were generated from the Nurses' Health Study

originally conducted by Belanger et al. [71], a well-designed high quality cohort study of the factors affecting women's health. The results of this study show an increased risk of ovarian cancer at the three highest exposure categories in this study, with the risk at the lowest exposure level [OR: 1.15 (95% CI: 0.89 to 1.47)] being numerically, although not significantly, elevated. Other studies in Table 4 have provided findings in support of an exposure response based on increasing number of talc applications [20, 30, 34].

In order to permit more direct comparisons of the exposure-response findings from these studies, and whenever the original study data permits, we standardized exposure measurements into talc-years as shown in Figure 3. Data points were selected from studies after excluding potential data points that are lacking precise information on the level of exposure to talc. The mid-point of the exposure categories in the exposure-response studies was used for exposure-response assessment.

Overall, the graphical results shown in this Figure 3 suggest a possible increasing trend in ovarian cancer risk with increasing cumulative exposure to talc; however, there is also a high degree of uncertainty surrounding many of the individual risk estimates. (A formal statistical test for trend was not attempted because of the high degree of heterogeneity among studies noted previously in our meta-analysis discussed in section 3.4.)

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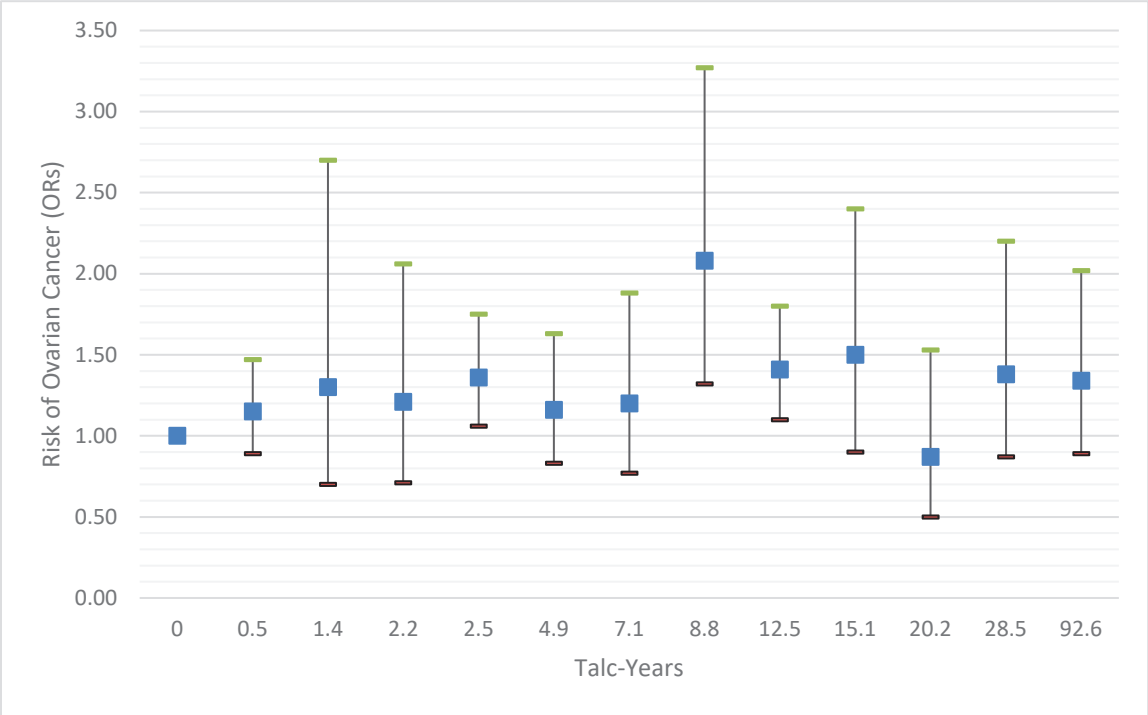

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400 **Figure 3: Ovarian cancer risk estimates at increasing levels of exposure to talc, as**
401 **reported from multiple studies**

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405 **Table 4: Summary of studies that reported ORs for increasing number of lifetime perineal talc applications**

Study	Stratification	Reported Exposure-Response Strata	aOR*	95% CI
Schildkraut et al. (2016) [30]	Lifetime genital powder	<3,600 applications, any genital use vs (never use)	1.16	[0.83, 1.63]
		>3,600 applications, any genital use vs (never use)	1.67	[1.23, 2.26]
Whittemore et al. (1988) [32]	Overall trend	Overall trend for 30 uses per month	1.3	[0.88, 1.92]
Wu et al. (2009) [34]	By total times of talc use	≤ 5,200 times vs nonuse	1.2	[0.77, 1.88]
		5,201 – 15,600 times vs nonuse	1.38	[0.87, 2.20]
		15,601 – 52,000 times vs nonuse	1.34	[0.89, 2.02]
		> 52,000 times	1.99	[1.34, 2.96]
Mills et al. (2004) [25]	By cumulative use (frequency × duration)	First quartile (lowest exposure)	1.03	[0.59, 1.80]
		Second quartile	1.81	[1.10, 2.97]
		Third quartile	1.74	[1.11, 2.73]
		Fourth quartile (highest exposure)	1.06	[0.62, 1.83]
Rosenblatt et al. (2011) [29]	By lifetime number of applications of perineal powder after bathing	1-1,599 applications	1.21	[0.71, 2.06]
		1,600-4,799 applications	2.08	[1.32, 3.27]
		4,800-9,999 applications	0.87	[0.50, 1.53]
		≥10,000 applications	0.87	[0.48, 1.57]
Cramer et al. (2016) [15]	By total genital applications	≤360 total genital applications	1.15	[0.89, 1.47]
		361-1,800 total genital applications	1.36	[1.06, 1.75]
		1,801-7,200 total genital applications	1.41	[1.10, 1.80]
		>7,200 total genital applications	1.39	[1.11, 1.75]
Harlow et al. (1992) [20]	Total Lifetime Perineal Applications*	< 1,000 applications	1.3	[0.7, 2.7]
		1,000 - 10,000 applications	1.5	[0.9, 2.4]
		>10,000 applications	1.8	[1.0, 3.0]

406 * aOR: adjusted odds ratio

407 ** 10,000 applications are equivalent to daily use for 30 year

4. Discussion

The present analysis of the association between perineal use of talc powder and ovarian cancer risk considered four decades of scientific work exploring the epidemiological associations and non-human studies. The motivation for this review is based on two questions: what do human epidemiology studies of perineal talc exposure reveal about potential ovarian carcinogenicity, and what do in-vitro and in-vivo studies suggest about potential mechanisms of toxicity?

A systematic review of the human epidemiology studies was conducted to address the first question. Thirty observational epidemiologic studies were identified and assessed for quality using the NOS [6]. In parallel with the review of human epidemiological evidence, a (non-systematic) review of evidence exploring in vitro and in vivo toxicology data on talc was conducted to explore how talc might produce biological changes. This latter review provides some insights concerning possible mechanisms of talc toxicity, including oxidative stress, immune system alterations and inflammatory responses. However, it also indicates that talc is not genotoxic. In total, the epidemiology studies suggest that perineal exposure to talc powder is a possible human ovarian carcinogen but there are concerns that the actual exposure experienced by these women over the past 40-50 years is not well understood. As reported by Langesth and colleagues [67], there had been some concern that asbestos-contaminated talc powder that was produced prior to 1976 might have been a confounder; however, the similarity of findings between studies published prior to and after this point suggests asbestos contamination does not explain the positive association between perineal use of talc powder and risk of ovarian cancer [25, 27].

Human observational studies have inherent limitations that could bias the findings. Potentially important sources of bias reported in the included studies include: 1) selection bias due to low response rates from cases and controls or from limiting subjects to English-speaking women of two specific races, and 2) exposure misclassification due to recall bias inherent in case control studies. Other limitations included small sample sizes in some studies, small numbers of subjects in subgroup analyses, lack of information on duration of talc use in many studies that only compared ever vs never users, as well as lack of information on the talc content of the different brands of genital powders used. In two of the three cohort studies, the follow-up period between exposure assessment and end of study could have been inadequate to detect a potential association between talc exposure and ovarian cancer. Houghton et al. [39] reported a mean follow up of 12.4 years, while Gates et al. [36] followed a cohort of women for 24 years. However, Gertig et al. [37] and Gonzalez et al. [38] noted that one of their main limitations is the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and ovarian cancer. For example, studies of smoking and ovarian cancer suggest that follow-up periods as long as four decades improve recognition of the carcinogenic effects of smoking [72]; longer follow up periods may also improve characterization of the association between talc and ovarian cancer. In this regard, the minimum latency period for radiation-induced ovarian cancer among Hiroshima atomic bomb survivors has been reported to range from 15 to 20 years [73, 74]. Common strengths reported in most studies were the selection of population controls in many of the case control studies and having relatively large sample sizes that allowed a multitude of stratified analyses.

Effect estimates in this meta-analysis were pooled from 24 case control studies and 3 cohort studies, and refer to ever vs never use of perineal talc. Pooling by study design showed a notably higher risk estimate for case-control [OR: 1.32 (95% CI: 1.24 to 1.40), P < 0.00001, I^2= 22%] compared to cohort studies [OR: 1.06 (95% CI: 0.9 to 1.25), P= 0.49, I^2= 17%]. Although the reasons for this are unclear, the difference could potentially be due to issues relating to latency, study power, or exposure misclassification.

Although cohort study designs are efficient for examining diseases with a long latency period, it is essential that the period between talc exposure and the cancer diagnosis be sufficiently long. Gonzalez et al. [38] suggested that the latency period for ovarian cancer is between 15 to 20 years. In the cohort studies included in this review, Houghton et al. [39] reported a mean follow up of 12.4 years while Gates et al. [36] followed a cohort of women for 24 years. Gertig et al. [37] and Gonzalez et al. [38] noted that one of their studies' main limitations was the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and ovarian cancer.

In addition, cohort studies included may have been underpowered to detect an odds ratio (relative risk) of 1.3 estimated from the case control studies. This was noted by Narod et al. [75], who suggest that cohorts of at least 200,000 women would be needed to reach statistical significance if the true odds ratio is 1.3. The cohort studies included in this review included much smaller cohort sizes, ranging between 41,654 and 78,630 women.

Finally, in cohort studies, talc exposure was assessed at cohort entry and was used as a measure of chronic talc use during follow up. It is possible that women who were not exposed to perineal talc at the time of cohort entry began using talc at a later time, and vice versa, possibly introducing non-differential misclassification of exposure, which could bias the risk estimate towards the null value of unity. Conversely, in the presence of differential exposure misclassification, a bias away from the null hypothesis could accentuate differences between the cohort and case-control studies.

4.1. Exposures and outcomes

All epidemiological studies included in our review evaluated the association between the perineal application of talc and subsequent diagnosis of ovarian cancer. Perineal vs body exposure is an important distinction, as the movement of talc is thought to follow an ascending path from the perineum through the vagina, uterus and fallopian tubes to the ovarian (as well as fallopian tube and peritoneal) epithelium.

Ovarian cancer is a common gynecologic malignancy in developed and developing countries. Risk factors for ovarian cancer include age, infertility, nulligravidity, endometriosis, hereditary ovarian cancer, tobacco and asbestos.

Protective factors for ovarian cancer include oral contraceptives, bilateral tubal ligation, salpingo-oophorectomy, hysterectomy, and breast feeding [76]. It is a difficult cancer to diagnose early, with approximately 60% of the individuals diagnosed after the cancer has metastasized from the pelvic region, where this cancer begins. In the meta-analysis, comparing ovarian cancer risk among women who used talc versus those who

never used talc (using both case-control and cohort designs), we observed an approximate 30% increase in ovarian cancer risk in the group who used talc. The most common type of ovarian cancer seen in the general population, and among the women exposed to talc were of epithelial origin, most common histologic type (accounting for about 95% of all cases in the general population), and of serous morphology, the most common subtype (comprising about 75% in the general population).

The cell-type of origin and morphology of talc induced ovarian cancer is similar to that observed in typical ovarian cancer with approximately 95% derived from epithelium (from fallopian tube fimbriae, ovarian or peritoneal) with serous tumors as the most common subtype. Like most ovarian cancers, those associated with talc exposure are typically diagnosed late in the course of the disease (~60% are diagnosed after the disease has spread outside of the pelvis). This late diagnosis complicates our understanding of the history and origin of the disease.

Demographic factors were analyzed using subgroup analysis where possible, and these were generally consistent with what has been previously observed with respect to ethnicity and risk of ovarian cancer. Additionally, these data also provide support for a mechanism of ovarian cancer induction working via an inflammatory pathway associated with oxidative stress [27, 77, 78].

A small number of studies explored the issue of ethnicity: Asians (1 study), Hispanics (2 studies), and African-Americans and Whites (3 studies each). Among these studies the risk for talc associated ovarian cancer was 1.70 (Hispanics), 1.67 (African Americans), 1.28 (Whites) and 0.04 (Asians). These risk factors compare with the demographics of ovarian cancer in the US population with an overall prevalence of

ovarian cancer of 12.7/100,000 among Whites 13.4/100,00, Hispanics 11.3/100,000, African Americans 9.8/100,000, and Asians 9.8/100,000. The difference in US prevalence and risk of talc induced ovarian cancer among Hispanics and African Americans may provide further evidence concerning exposures or mechanism of action [76].

A variety of factors were assessed with respect to the studies contributing to the meta-analysis, including study quality (NOS) and publication year. In general, the risk of talc associated ovarian cancer was similar among studies with an NOS ≥7 or NOS <7. Year of publication also failed to demonstrate a significant impact on reported talc risk estimates.

4.2. Exposure metrics

Given that the epidemiological studies indicate that talc is a possible human carcinogen, we next evaluated the studies to identify those comparing differences in exposure. The initial assessment exploring frequency of use, utilized a qualitative exposure metric: low, medium and high. Ovarian cancer was observed to increase between the medium and high exposure groups, consistent with an exposure-response relationship. Several studies explored duration of use (years) and risk of ovarian cancer; 20+ years (2 studies),10 (5 studies), 10/20 (2 studies), and observed that the risk was greatest in the 20+ year exposure group, followed by lower risk in the 10/20 year and <10-year exposure groups.

Several studies explored the route of exposure or approach to talc application on ovarian cancer risk, including; hysterectomy, bilateral tubal ligation, diaphragm,

underwear, sanitary napkin, as these can provide insight into differences in exposure of the fallopian tube, ovarian and peritoneal epithelium. Use of a diaphragm, as well as tubal ligation act to interrupt exposure of perineal talc to reproductive tract. In contrast, application to underwear and sanitary napkin exposure will provide broader exposures. As hypothesized, the use of diaphragm and bilateral tubal ligation decreased ovarian cancer risk [22].

4.3. Modifying Factors

Modifiers of the risk of ovarian cancer, either associated with talc exposure, or a spontaneous disease, can provide clues to potential mechanisms of causation. Menopausal status and use of hormones can modify the risk for ovarian cancer. For example, among post-menopausal women receiving hormonal therapy the risk for ovarian cancer is greater than those who are premenopausal and those who are post-menopausal not receiving hormone therapy. It has also been observed that women receiving fertility treatment who do not become pregnant are at greater risk for ovarian cancer [22]. These data suggest that hormonal status (elevated estrogens and/or gonadotropins) plays a role in the mechanism of action of talc associated ovarian cancer.

Subgroup analyses in the meta-analysis indicated that interruption of the pathway from perineum to pelvis (as with bilateral tubal ligation or use of diaphragm) decreased risk for ovarian cancer. This supports the hypothesis that talc acts by local action on the ovary. Given the data developed in non-human studies suggesting an inflammatory response of epithelial cells to talc, and histological observations

corroborating those observations, additional support for an inflammatory pathway leading to ovarian cancer is provided. One study recently explored the use of anti-inflammatory drugs and observed a decreased risk for ovarian cancer, also supporting the importance of an inflammatory pathway with oxidative stress [77].

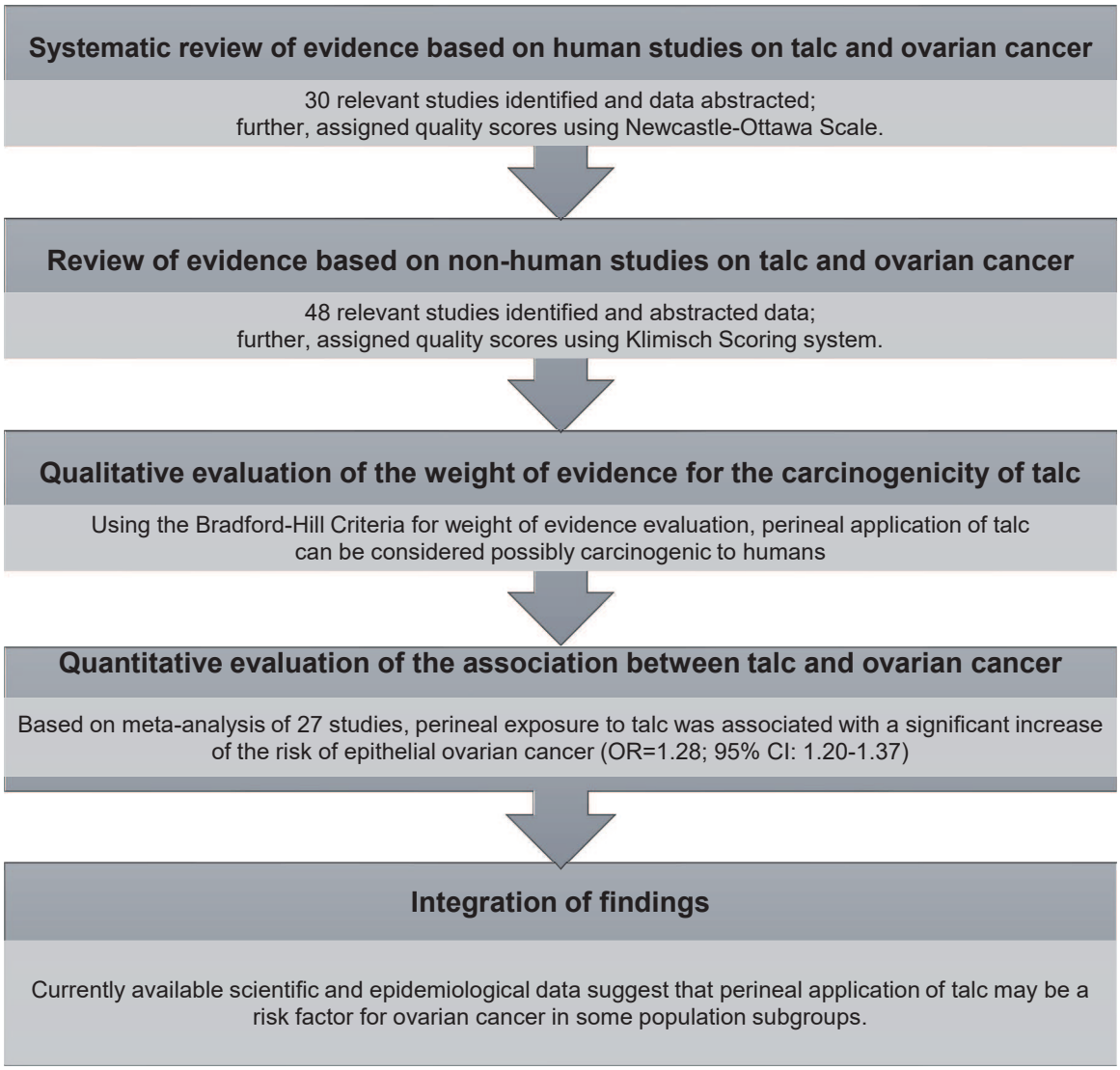

Figure 4: Detailed process flow for assessment of talc carcinogenicity

5. Conclusion

We conducted an extensive search, examination, assessment and analysis of evidence from published human and non-human original as well as all published reviews that considered the association between genital/perineal use of talc powder and risk of ovarian cancer. The steps followed in conducting this review are summarized in Figure 4, along with the key findings at each step. Consistent with previous evaluations the IARC in 2010 [2], and subsequent evaluations by individual investigators [3, 5, 69], the present comprehensive evaluation of all currently available relevant data indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans.

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D. Krewski is the Natural Sciences and Engineering Council of Canda Chair in Risk Science at the University of Ottawa, and Chief Risk Scientist for Risk Sciences International (RSI), a Canadian company established in 2006 in partnership with the University of Ottawa (www.riskciences.com). Dr. Mohamed Kadry Taher, Ms. Nawal Farhat, and Dr. Donald Mattison report personal fees from RSI in relation to this work. A preliminary version of this paper was presented at the National Cancer Institute Directors' Meeting held in Lyon, France on July 11-13, 2018 and benefited from comments provided by international experts attending that meeting.

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